BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JULY, 1943

ROLE OF THE KIDNEY IN THE GENESIS OF HYPERTENSION*

HOMER W. SMITH, WM. GOLDRING AND HERBERT CHASIS

The Departments of Physiology and Medicine, New York University College of Medicine, New York City

My position on this program is suggestive of the role of an intermediary between exploratory investigation and practical medicine. Whether or not it was the intention of the program committee, I am sandwiched between theory and practice and shall endeavor to discharge my responsibilities by discussing the evidence for and against the belief that the kidneys are primarily responsible for the genesis of essential hypertension.

For some years a group of investigators at New York University College of Medicine have been studying this question from the point of view of the renal circulation. William Goldring, Herbert Chasis and Hilmert Ranges are the investigators concerned, and I must emphasize to you that I appear here tonight merely in the capacity of a spokesman for my colleagues. Not only am I indebted to them with respect to published investigations, but at my request Goldring and Chasis have prepared for me the digest of literature which I shall later review. Needless to say, however, we are in complete agreement in respect to interpretation and I gladly assume the responsibility for what I have to say.

* Read at the Stated Meeting of The New York Academy of Medicine, February 4, 1943.

As a physiologist and a neutral observer of the pros and cons in the long-standing debate on the role of the kidney in hypertension, I have no subjective reasons for pulling my punches.

Last year we published a study of the effective renal blood flow in sixty subjects with essential hypertension, many of whom had been followed for a considerable period of time.[1] We emphasized that the renal blood flow by itself is an unreliable datum since the quantity of functional renal parenchyma in various individuals, and especially in individuals with diseased kidneys, varies considerably. Consequently in that report the quantity of functional renal parenchyma present in each subject was evaluated by means of the saturation method and the effective blood flow was in each case referred to this primary datum. The resulting ratio of the effective blood flow per unit of residual functional tissue is remarkable for its constancy in normal subjects, and it constitutes an index to which considerable significance, in our opinion, may be attached in subjects with vascular or renal disease.

Omitting the finer technicalities of that study, we concluded that our evidence was against the belief that renal ischemia exists primary to the development of essential hypertension. It is true that renal ischemia is present in many hypertensive subjects, but this ischemia appears to be a result of the presence of vasoconstrictor substances in the blood, since it is readily reversible by agents which produce renal hyperemia in normal subjects, and during induced hyperemia the effective blood flow per unit of functional rental tissue is of the same order of magnitude in hypertensive subjects as in normals. The ischemic tendency is still present after renal denervation, which is why we think that it is of humoral origin.

It does not advance our problem, and it is of course illogical, to suppose at one moment that humoral agents are operating to reduce renal blood flow and then at the next moment to suppose that the reduction in renal blood flow is the reason for the appearance of these agents in the blood.

An even more cogent line of evidence is available in a second study made by Chasis and Redish[2] of the effective renal blood flow in the separate kidneys of twenty-one hypertensive patients. If it is predicated that renal ischemia is the primary causal factor underlying essential hypertension, the factors giving rise to this ischemia must be sought in anatomical faults which obstruct some greater or lesser fraction of the

renal circulation. By the laws of chance, and in accordance with the experience of pathologists, such obstructions would not be distributed symmetrically nor would they, except in rare instances, affect the renal blood flow symmetrically. Consequently, unilateral ischemia should be observed much more frequently than symmetrical bilateral ischemia. Yet among these twenty-one hypertensive patients the effective blood flow per unit of functional tissue was, within limits of variability no greater than are observed among normals, identical on the two sides. Not a single one showed unilateral impairment. This result is compatible only with the view that the ischemic tendency operates equally upon the two kidneys, and it is difficult to see how this could be the case if ischemia *per se* is the beginning of the story.

Proponents of the ischemic theory sometimes obscure the argument by hypothesizing that in essential hypertension a multitude of microscopic Goldblatt clamps have been placed upon the finer renal arterioles. But this is a begging of the question. If we are to respect the meaning of words and the sequences of pathology, then those who would put clamps upon all or a large fraction of the renal arterioles must forthwith abandon the primacy of renal ischemia in the argument of causation, and accept the primacy of arteriolar disease of as yet unidentified origin.

To summarize these clinical studies, then, the renal ischemia which is present in some hypertensive subjects affects both kidneys equally; it is of a physiological, reversible nature except in very late stages, and under reversal a hyperemia as good as is enjoyed by normal kidneys results; it appears to be of humoral origin, since denervation does not abolish it. Faced with these facts we interpret the observed renal ischemia as one of the sequelae of the disease, and not its cause. The renal arterioles in man appear to be rather more sensitive normally to vasoconstrictor agents than they are in the dog, the only other well-studied species. It would be profitable, perhaps, to make in man a quantitative study of the relative sensitivity of the renal arterioles as compared with those of the skin and muscle mass.

From this point, then, let us reword our problem by asking what is the evidence that the kidneys play any part in the origin of hypertension? There comes to your mind immediately, no doubt, the Goldblatt experiment, and I would answer this apparently convincing argument by saying that this is only reasoning by analogy. I will reply by drawing an analogy. Had someone applied a clamp to the pancreatic

artery before the days of Minkowsky and obtained diabetes (and I have no doubt but what the judicious application of a clamp to the pancreatic artery would produce some form of diabetes or at least glycosuria), there would have come into existence the theory that diabetes was due to pancreatic ischemia. We know, of course, that that is not so and indeed it is probably the very rare case in which pancreatic ischemia plays any part. When Minkowsky took out the pancreas and obtained diabetes, there came into existence the theory that diabetes in the historic and literal sense of glycosuria, is due solely and simply to an underproduction of insulin. We now know that this is not true. The essential clinical signs and symptoms commonly identified as diabetes, i.e., decreased glucose tolerance and glycosuria, may be brought into existence by disturbances in the pituitary gland, in the liver, and possibly in the adrenal cortex, in animals and individuals in which the pancreas is not primarily at fault, whatever intermediary role the pancreas may play. What, then, are the causes of diabetes? They are multiple, and in no instance do we yet know the whole answer. The Goldblatt experiment shows that you can produce hypertension in the dog by renal ischemia. The experiment in principle is unquestionably applicable to man, but it proves nothing logically about the sequence of events in that large group of patients who have so-called "essential hypertension."

What other evidence is there to indict the kidneys? There come to mind numerous papers published in the last few years which, whatever their intent, give the impression of demonstrating that unilateral renal disease is causally related to a hypertensive process. The proof consists in the purported reduction of the hypertension by the removal of the offending kidney. There is, unfortunately, no criterion of the presence or intensity of hypertensive disease except the elevation of the blood pressure itself, or the subjective distress and eye-ground changes which are presumed to be sequelae of the elevated blood pressure; and blood pressure is an extraordinarily complex dynamic product of the circulation in which changes are difficult to interpret even under optimal conditions for the most precise study. I need not dwell upon the lability of the blood pressure in many hypertensive subjects, since this lability has been discovered by every investigator who has attempted to work under controlled conditions.

But because of the importance which this surgical-pathological literature assumes in the general impression, I have asked my colleagues

TABLE I

UNILATERAL NEPHRECTOMY

Papers.....25	*Cases*	*Per cent*
Cases	76	100
Negative results reported	39	51
Positive results reported	37	49
Of these, 30 are incorrectly appraised because:		
a. BP did not fall into normal range	8	27
b. Inadequate control	1	3
c. Inadequate postoperative follow-up	19	63
d. BP returned to hypertensive level in 6 months	2	7
Final appraisal: Negative results	69	91
Positive results	7	9

to review it *in toto* and to appraise it critically under rigid but reasonable specifications.*

It is convenient to break this literature into several categories, the first of which consists of those papers, 25 in number,[3-27] in many of which a reduction in blood pressure has been reputed to follow unilateral nephrectomy, the removal of the kidney being indicated by demonstrated or suspected unilateral renal disease (Table I). Seventy-six cases are reported in these 25 papers, and in 51 per cent of these cases the authors themselves report negative results in respect to blood pressure reduction. Of the 49 per cent in which a positive result was obtained in the authors' opinion, 30 cases are held by my colleagues to be incorrectly appraised either because the blood pressure did not fall into the normal range, because there was an inadequate control study to establish true hypertension, because there was inadequate postoperative follow-up, or because the blood pressure was shown to return to hypertensive levels within six months. So in the final appraisal, out of the total of these 76 cases, unilateral nephrectomy has had a favorable result in respect to the reduction in blood pressure in 7 cases only.[3, 7, 9, 14, 17, 18, 19] Accepting these 7 cases on their face value, in only one case in ten in which the thesis has been tested by nephrectomy is there evidence that the hypertensive process has its origin in disease of one kidney.

* A detailed discussion of criteria, etc. will appear in a subsequent publication.

TABLE II

ALLEGED COMPRESSION OF THE RENAL ARTERY OR RENAL PARENCHYMA

Obstruction of renal artery	7
Renal compression	3
Total	10
Hypertension may have preceded plaque	1
Questionable compression of renal artery by aortic aneurysm	1
Bilateral renal disease not excluded	2
Blood pressure did not fall after nephrectomy	2
Unsatisfactory	6
Apparently satisfactory	only 4 in entire literature

The second category deals with instances of hypertension supposedly arising from mechanical compression of the renal circulation or the renal parenchyma (Table II). There are a total of 10 cases in the literature,[6, 7, 15, 17, 27, 28, 29, 30, 31, 32] seven of which had obstruction of one sort or another of the renal artery, while 3 had renal compression. On reviewing these records, one must be discarded because there was a possibility that hypertension may have preceded the formation of the plaque which at necropsy was discovered in the renal artery; one was a suppositious compression of the renal artery by an aortic aneurysm, but being suppositious, is scarcely admissable as positive evidence. In two cases bilateral renal disease was not excluded, and in one of these it was quite definitely indicated. In two cases the blood pressure did not fall after nephrectomy, indicating that when put to the final test the assumed explanation failed to work. This leaves us with 4 cases only in the entire literature in which apparently satisfactory correlation is established between gross obstruction of the renal circulation and hypertension. We accept these 4 cases at their face value as demonstrating the applicability of the Goldblatt experiment to man, without generalizing beyond the limited evidence.

Turning now to the other aspects of the problem, we come to the third category of papers in which it is claimed that there is an abnormally high incidence of urologic disease in hypertensive subjects (Table III). Schroeder and Steele[33] have reported 113 urologic anomalies out

TABLE III

INCIDENCE OF UROLOGIC DISEASE IN HYPERTENSION

Schroeder and Steele (1941) report 113/250 positives among living patients, or 45 per cent. Of these:

53 had bilateral renal disease:
8 had glomerulonephritis
17 had bilateral abnormal pyelogram
28 probable renal disease

Leaving 60/250 possible unilateral disease, or 24 per cent.

Wosika, Jung and Maher (1942) report 227/568 positives in necropsies, or 40 per cent, including all types of unilateral and bilateral disease, with no break-down.

of 250 living patients with hypertension, or a 45 per cent incidence of urologic fault. We exclude from this list 53 who had bilateral renal disease; 8 who had glomerulonephritis, 17 with bilaterally abnormal pyelograms, and 28 in whom renal disease was suspected but not proven. This leaves 60 patients with apparent urological fault out of 250 hypertensives, or 24 per cent. However, the judgment of urologic fault in this series was based largely upon abnormal radiograms obtained by intravenous or retrograde pyelography, and it has been our experience that the diagnosis of abnormality in a pyelogram is a very hazardous matter, since an innocuous angulation of the ureter or dilatation of the pelvis can give the visual impression of significant abnormality, although there is actually no obstruction of the lumen or evidence of renal impairment. The incidence of such apparent abnormalities in adults giving no history or evidence of abnormal renal function or of hypertension is very large. The significance of many of the residual 60 cases in Schroeder and Steele's series is therefore open to some doubt.

Wosika, Jung and Maher[34] have reported 227 urologic abnormalities out of 568 necropsies of hypertensive subjects, or an incidence of 40 per cent. These authors, however, include all types of unilateral and bilateral disease, and since they offer no break-down it is impossible to evaluate even the approximate significance of this figure with respect to the relation between unilateral diseases and hypertension.

The fourth category of paper deals with the incidence of hypertension in pyelonephritis (Table IV). In 500 cases of pyelonephritis, Pearman, Thompson and Allen[35] found that only 9 per cent had hyper-

TABLE IV

INCIDENCE OF HYPERTENSION IN

Cases		*Per cent with Hypertension*
500	Pyelonephritis (unilateral & bilateral)	9.0
500	Goitre without hyperthyroidism	10 0
500	Gall-bladder disease	7.0

From Pearman, Thompson and Allen[35]

TABLE V

INCIDENCE OF HYPERTENSION IN UROLOGIC DISEASE

	Per cent with Hypertension
1. Friedman, Moschkowitz and Marrus[18]	
193 unilateral renal disease proven at operation	21.8
1006 living controls	22 8
2. Oppenheimer, Klemperer and Moschkowitz[21]	
79 necropsied patients with unilateral renal disease	27.5
333 control necropsies	24.0
3. Baggenstoss and Barker[36]	
97 necropsied patients with unilateral renal disease	29.3
100 control necropsies	29.0
4. Braasch, Walters and Hammer[37]	
1684 living patients with surgical uropathology	18.7
975 living controls	20.0
5. Crabtree and Chaset[16]	
150 nephrectomies for unilateral renal disease	9.0
(1981 living controls from 1 and 4)	21.4
(433 necropsy controls from 2 and 3)	26.5

tension, a figure that compares favorably with goitre without hyperthyroidism and with gall-bladder disease. This result is wholly incompatible with the belief that unilateral pyelonephritis tends to cause hypertension.

The last category of paper examines the incidence of hypertension in patients with demonstrated unilateral renal disease (Table V). Friedman, Moschkowitz and Marrus[18] found an incidence of hypertension of 21.8 per cent in 193 patients with unilateral renal disease proven at operation. This figure is lower than the 22.8 per cent incidence which

these authors found in a control series of 1006 living patients. Again Oppenheimer, Klemperer and Moschkowitz[21] found a 27.5 per cent incidence of hypertension in 79 necropsies where unilateral renal disease was demonstrated, a figure not significantly above the 24 per cent of hypertension which they found in 333 control necropsies. Baggenstoss and Barker[36] similarly found an identical incidence of hypertension in patients with and without unilateral renal disease, while Braasch, Walters and Hammer[37] found 18.7 per cent incidence of hypertension in 1684 living patients with surgical uropathology, a figure slightly less than in their 975 living controls. Lastly, Crabtree and Chaset[16] found only 9 per cent incidence of hypertension in 150 patients who had suffered nephrectomy for unilateral disease. Combining the living controls in 1 and 4 (Table V) the incidence of hypertension should have been 21.4 per cent, or considering the necropsy controls in 2 and 3, the incidence should have been 26.5 per cent. These figures are of the order of magnitude accepted by most medical statisticians as designating the incidence of hypertension in the adult population. Obviously, in Crabtree and Chaset's 150 patients, unilateral renal disease had exerted a very favorable influence on the frequency of high blood pressure!

The data summarized in this Table are impressive in their statistical demonstration that unilateral renal disease and surgical uropathology do not predispose to hypertension. Add to them the data from Pearman, Thompson and Allen in Table IV, with 9 per cent hypertension in 500 pyelonephritics, and the argument for renal origin appears tenuous indeed. The positive evidence on critical review boils down to seven cases in whom unilateral nephrectomy apparently effected a reduction in blood pressure and four cases in which a gross obstruction or compression of the renal circulation could have accounted for the hypertensive process, and we have in the recorded literature eleven cases in favor of the argument.

We conclude, therefore, that unilateral renal disease is rarely a cause of hypertension in man.

But how about bilateral renal disease? You will recall that it was Richard Bright[38,39] who first associated the elevation of blood pressure with kidney disease. He was impressed by the left ventricular hypertrophy of nephritis and allied diseases, and even in the absence of methods for measuring blood pressure, he deduced that there must be an increased load thrown upon the heart, and inferred that this load was

due to the resistance offered to blood flow by the kidneys. Later Johnson[40] and after him Gull and Sutton[41] demonstrated that in hypertension arterioles in other organs in the body were frequently narrowed as well, and then Allbutt[42] and Huchard[43] demonstrated that hypertension could exist in the absence of sclerosis of either the renal or systemic arterioles. From this observation, frequently confirmed, arose the conception that hypertension could exist in the absence of renal or systemic arteriolosclerosis, and consequently the aggregation of diseases formerly called "Bright's disease" was divided into those in which the kidneys were primarily involved, i.e., glomerulonephritis, polycystic renal disease and pyelonephritis, and those in which the kidneys were involved only secondarily to the hypertension. Hence the latter came to be called "essential hypertension." It seems to us that this division is still warranted.

But why does the blood pressure rise in glomerulonephritis, bilateral polycystic renal disease and bilateral pyelonephritis, if the kidneys are not primarily responsible for the pathological process in the large majority of patients with essential hypertension? The answer to this question can be identical with the answer which we have opposed to generalizing from the Goldblatt experiment: the kidneys can be the cause of elevated blood pressure where both organs are initially diseased, and in rare cases where only one kidney is affected, though whether the significant perturbation here is renal ischemia or some breakdown in renal metabolic activity cannot as yet be said; but the acceptance of this fact must not lead us into accepting the rare explanation for the general rule. The statistics are against it: hypertension has no higher incidence with unilateral renal disease than in the general population, and in the unilateral nephrectomies so far reported, in the opinion of the authors 50 per cent are improved, by our accounting only 10 per cent. In the nature of the problem, the true improvement is probably less.

It seems to us, therefore, that under the surgical and pathological evidence, as under the physiological evidence, the theory of primary renal origin is unproved. So far as the genesis of essential hypertension is concerned, the kidney appears to be the victim rather than the culprit. This is not to argue, however, that if the genesis is complex the kidney may not play an intermediary role, even as the pancreas may play a role in all perturbations of carbohydrate metabolism. But to ven-

ture in this direction is pure speculation. At this moment the origin of essential hypertension is unknown.

REFERENCES

1. Goldring, W., Chasis, H., Ranges, H. A. and Smith, H. W. Effective renal blood flow in subjects with essential hypertension. *J. Clin. Investigation,* 1941, *20:*637.
2. Chasis, H. and Redish, J. Effective renal blood flow in the separate kidneys of subjects with essential hypertension. *J. Clin. Investigation,* 1941, *20:*655.
3. Butler, A. M. Chronic pyelonephritis and arterial hypertension, *J. Clin. Investigation,* 1937, *16:*889.
4. Boyd, C. H. and Lewis, L. G. Nephrectomy for arterial hypertension; preliminary report, *J. Urol.,* 1938, *39:*627.
5. Barker, N. W. and Walters, W. Hypertension associated with unilateral chronic atrophic pyelonephritis; treatment by nephrectomy, *Proc. Staff Meet., Mayo Clinic,* 1938, *13:*118.
6. Bradley, J. E. and Pincoffs, M. C. Association of adeno-myo-sarcoma of kidney (Wilm's tumor) with arterial hypertension, *Ann. Int. Med.,* 1938, *11:*1613.
7. Leadbetter, W. F. and Burkland, C. E. Hypertension in unilateral renal disease, *J. Urol.,* 1938, *39:*611.
8. Crabtree, E. G. Hypertension in destructive infected unilateral lesions of the kidney, *Tr. Am. A. Genito-Urin. Surgeons,* 1938, *31:*299.
9. Barney, J. D. and Suby, H. I. Unilateral renal disease with arterial hypertension; report of a case apparently cured following nephrectomy, *New England J. Med.,* 1939, *220:*744.
10. Mulholland, S. W. Hypertension's challenge to urology, *J. Urol.,* 1939, *42:*957.
11. Bothe, A. E. Pyelonephritis in children and adults with hypertension, *J. Urol.,* 1939, *42:*989.
12. Barker, N. W. and Walters, W. Hypertension and chronic atrophic pyelonephritis; results of nephrectomy, *J. A. M. A.,* 1940, *115:*912.
13. Schroeder, H. A. and Fish, G. W. Studies on "essential" hypertension; effect of nephrectomy upon hypertension associated with organic renal disease, *Am. J. M. Sc.,* 1940, *199:*601.
14. Patch, F. S., Rhea, L. J., Codnere, J. T. Hypertension in a girl of 12, associated with unilateral, chronic, atrophic pyelonephritis; treated by nephrectomy, *Canad. M. A. J.,* 1940, *43:*419.
15. Nesbit, R. M. and Ratliff, R. K. Hypertension associated with unilateral nephropathy, *J. Urol.,* 1940, *43:*427.
16. Crabtree, E. G. and Chaset, N. Vascular nephritis and hypertension; combined clinical and clinicopathologic study of 150 nephrectomized patients, *J.A.M.A.,* 1940, *115:*1842.
17. Farrell, J. I. and Young, R. H. Hypertension caused by unilateral renal compression, *J.A.M.A.,* 1942, *118:*711.
18. Friedman, B., Moschkowitz, L. and Marrus, J. Unilateral renal disease and renal vascular changes in relation to hypertension in man, *J. Urol.,* 1942, *48:5.*
19. Kennedy, R. L. J., Barker, N. W. and Walters, W. Malignant hypertension in a child; cure following nephrectomy. *Am. J. Dis. Child.,* 1941, *61:*128.
20. Abeshouse, B. S. Hypertension and unilateral renal disease; review of literature and report of 16 cases, *Surgery,* 1941, *9:*942; *10:*147.
21. Oppenheimer, B. S., Klemperer, P. and Moschkowitz, L. Evidence for Goldblatt mechanism of hypertension in human pathology, *Tr. A. Am. Physicians,* 1939, *54:*69.
22. McIntyre, D. W. Unilateral chronic pyelonephritis with arterial hypertension; apparent cure after nephrectomy, *J. Urol.,* 1939, *41:*900.
23. Everett, H. S. Hypertension in unilateral renal disease, *Urol. & Cutan. Rev.,* 1940, *44:*557.
24. Weiss, E. *Unpublished data.*
25. Jeck, H. and Hotchkiss, R. *Unpublished data.*
26. Hotchkiss, R. *Unpublished data.*

27. Howard, T. L., Forbes, R. P. and Lipscomb, W. R. Aneurysm of left renal artery in a child 5 years old with persistent hypertension, *J. Urol.*, 1940, *44:* 808.
28. Freeman, G. and Hartley, G., Jr. Hypertension in patients with solitary ischemic kidney, *J.A.M.A.*, 1938, *111:* 1159.
29. Hoffman, B. J. Renal ischemia produced by aneurysm of abdominal aorta, *J. A. M. A.*, 1942, *120:*1028.
30. Blatt, E. and Page, I. H. Hypertension and constriction of renal arteries in man; report of a case, *Ann. Int. Med.*, 1939, *12:*1690.
31. Prinzmetal, M., Hiatt, N. and Tragerman, L. J. Hypertension in patient with bilateral renal infarction; clinical confirmation of experiments in animals, *J.A.M.A.*, 1942, *118:*44.
32. Saphir, O. and Ballinger, J. Hypertension (Goldblatt) and unilateral malignant nephroscelerosis, *Arch. Int. Med.*, 1940, *66:*541.
33. Schroeder, H. A. and Steele, J. M. Studies on "essential" hypertension; association of hypertension with organic renal disease, *Arch. Int. Med.*, 1941, *68:* 261.
34. Wosika, P. H., Jung, F. T. and Maher, C. C. Urologic hypertension as an entity, *Am. Heart J.*, 1942, *24:*483.
35. Pearman, R. O., Thompson, G. J. and Allen, E. V. Urographic evidence of renal lesions in series of patients suffering from essential hypertension, *Proc. Staff Meet., Mayo Clin.*, 1940, *15:*467.
36. Baggenstoss, A. H. and Barker, N. W. Unilateral renal atrophy associated with hypertension, *Arch. Path.*, 1941, *32:*966.
37. Braasch, W. F., Walters, W. and Hammer, H. J. Hypertension and surgical kidney, *J.A.M.A.*, 1940, *115:*1837.
38. Bright, R. *Reports of medical cases selected with a view of illustrating the symptoms and cure of diseases by a reference to morbid anatomy.* London, Longman, 1827-31, v. *2,* p. 3.
39. Bright, R. Tabular view of the morbid appearances in 100 cases connected with albuminous urine with observations, *Guy's Hosp. Rep.*, 1836, *1:*380.
40. Johnson, G. On certain points in the anatomy and pathology of Bright's disease of the kidney; the influence of the minute blood-vessels upon the circulation, *Med-Chir. Tr.*, 1868, *51:*57.
41. Gull, W. W. and Sutton, H. G. On the pathology of the morbid state commonly called chronic Bright's disease with contracted kidney, (arteriocapillary fibrosis), *Med-Chir. Tr.*, 1872, *55:*273.
42. Allbutt, C. Senile plethora or high arterial pressure in elderly persons, *Abstr. Hunterian Soc. Tr.*, 1895-96: 38.
43. Huchard, H. *Traité clinique des maladies du coeur et de l'aorte.* Paris, Doin 1899-1903, v. *3.*